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FORMULATION AND CHARACTERIZATION OF SURFACE MODIFIED DRUG DELIVERY SYSTEM BEARING SUMATRIPTAN

Aaditya Saini, Sunil Kumar Jain, Vivek Kumar Jain, Mansha Singhai, Rupesh Kumar Jain*

Adina Institute of Pharmaceutical Science, Sagar (M.P.)

***Correspondence Info:**
Rupesh Kumar Jain
Adina Institute of Pharmaceutical Science, Sagar (M.P.)
Email: rupeshjain856@gmail.com

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ABSTRACT

The present study focuses on the formulation and characterization of mucoadhesive nanoparticles of Sumatriptan for enhanced nasal drug delivery. Sumatriptan, a selective serotonin receptor agonist, is widely used in the treatment of migraine but suffers from poor oral bioavailability due to extensive first-pass metabolism. To overcome this limitation, mucoadhesive nanoparticles were developed using chitosan and sodium tripolyphosphate via the ionic gelation method. A series of six formulations (F1–F6) were prepared and evaluated for percentage yield, drug entrapment efficiency, particle size, zeta potential, mucoadhesive strength, and *in vitro* drug release. Among the formulations, F6 was found to be optimal, exhibiting a high percentage yield (83.32%), drug entrapment efficiency (80.32 ± 0.54%), and mucoadhesive strength (78.98 ± 0.85%). The optimized formulation showed spherical morphology with a uniform particle distribution under scanning electron microscopy and a particle size in the acceptable nanoscale range. *In vitro* drug release studies demonstrated a sustained release of Sumatriptan up to 12 hours, with 99.02% cumulative drug release. The release kinetics followed the Korsmeyer-Peppas model, indicating a non-Fickian mechanism involving both diffusion and polymer matrix erosion. These findings suggest that chitosan-based mucoadhesive nanoparticles could serve as an efficient nasal delivery system for Sumatriptan, potentially improving its bioavailability and therapeutic efficacy in migraine treatment.

Keywords: Sumatriptan, Mucoadhesive nanoparticles, Chitosan, Nasal drug delivery, Ionic gelation, Drug entrapment, In vitro release, Migraine therapy, Zeta potential, Mucoadhesion.

INTRODUCTION

Migraine is a chronic neurovascular disorder characterized by recurrent episodes of moderate to severe headaches, often accompanied by nausea, photophobia, and phonophobia. The underlying pathophysiology is believed to involve vasodilation of intracranial extracerebral blood vessels, triggering the activation of trigeminal sensory pathways (Goadsby *et al.*, 2017). Sumatriptan, a selective 5-HT_{1B/1D} receptor agonist, has emerged as the gold standard for the acute treatment of migraine due to its vasoconstrictive action and inhibition of pro-inflammatory neuropeptide release (Saxena *et al.*, 2006). However, its oral bioavailability is limited to approximately 15% owing to extensive hepatic first-pass metabolism and low permeability across gastrointestinal membranes (Plosker *et al.*, 1994).

To address these limitations, nanocarrier-based drug delivery systems have been explored.

Nanoparticles can enhance drug absorption, protect the drug from enzymatic degradation, and enable sustained drug release (Reddy *et al.,* 2004). Moreover, modifying the nanoparticle surface with hydrophilic or mucoadhesive polymers such as polyethylene glycol (PEG) or chitosan, respectively, can prolong circulation time, improve mucosal residence, and facilitate targeted drug delivery (Owens *et al.,* 2006).

Mucoadhesive delivery systems improve drug bioavailability by extending the residence time of the formulation at the mucosal surface. Chitosan, a natural polysaccharide obtained from chitin, is widely used for mucoadhesive nanoparticle preparation due to its biocompatibility, biodegradability, and ability to transiently open tight epithelial junctions (He *et al.,* 1999).

PEGylation, the covalent attachment of PEG to nanoparticles or drugs, reduces immunogenicity and opsonization while enhancing systemic circulation time, thus improving pharmacokinetic profiles (Veronese *et al.,* 2005).

The ionotropic gelation technique, which relies on the interaction of chitosan with counter-ions like sodium tripolyphosphate (STPP), is an efficient, mild method for fabricating nanoparticles, especially for sensitive drugs such as Sumatriptan (Calvo *et al.,* 1997). When combined with surface modification via PEG, this delivery strategy can result in a robust nanoparticulate system offering enhanced mucoadhesion and controlled drug release.

This study aims to formulate and characterize surface-modified chitosan nanoparticles bearing Sumatriptan to improve its mucosal retention, drug entrapment efficiency, and overall therapeutic efficacy in the management of migraine.

MATERIALS AND METHODS

Materials

The materials used for the formulation of Sumatriptan-loaded mucoadhesive nanoparticles included Sumatriptan, obtained from Pharmaceutical Company. Chitosan and sodium tripolyphosphate, essential for nanoparticle formation, were procured from Loba Chemie Pvt. Ltd., Mumbai. Additional reagents such as dipotassium hydrogen orthophosphate (Hi Media Pvt. Ltd., Mumbai), methanol, ethanol, chloroform, hydrochloric acid, and sodium hydroxide were also sourced from Loba Chemie and Jiangsu Huaxi International, Mumbai. All chemicals and reagents used were of analytical grade.

Methods

Formulation of surface modified drug delivery system of Sumatriptan

Chitosan nanoparticles were prepared using the ionotropic gelation method, as described by Lazaridou (2020), followed by surface modification with polyethylene glycol (PEG). Initially, a 1% (w/v) chitosan stock solution was prepared by dissolving chitosan in 1% (v/v) acetic acid at room temperature. For drug loading, 10 mg of Sumatriptan was dissolved in the chitosan solution under stirring.

A 1% (w/v) sodium tripolyphosphate (STPP) solution was prepared in distilled water and added dropwise into the chitosan-drug mixture under continuous magnetic stirring.

The resulting colloidal suspension was stirred for 30 minutes to allow crosslinking and nanoparticle formation. The formed nanoparticles were collected by filtration, rinsed with distilled water, and air-dried for 24 hours, followed by oven drying at 40°C for 6 hours.

For surface modification, the dried chitosan nanoparticles were resuspended in phosphate buffer (pH 7.4) and treated with methoxy-polyethylene glycol-succinimidyl carbonate (mPEG-SC) at a molar ratio optimized for PEGylation. The reaction mixture was stirred for 4 hours at room temperature to allow covalent attachment of PEG to the amine groups on the nanoparticle surface. Finally, the surface-modified nanoparticles were washed to remove unreacted PEG and dried for further use.

Evaluation of nanoparticles

Percentage Yield

The prepared nanoparticles with a size range of 100-150nm were collected and weighed from different formulations (Joysa, 2015). The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the nanoparticles.

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} x\ 100$$

% Drug Entrapment efficiency

The various formulations of mucoadhasive nanoparticles were subjected for entrapment efficiency. 10 mg of mucoadhasive nanoparticles from all batches were accurately weighed and crushed. The powder of nanoparticles were dissolved in 10 ml 6.8 pH phosphate buffer and centrifuge at 1000 rpm. This supernatant solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 6.8 pH phosphate buffer. The percentage drug entrapment was calculated using calibration curve method by UV Vis. Spectroscopy at 226 nm (Saha, 2010).

Measurement of mean particle size

The mean size of the nanoparticles was determined by photo correlation spectroscopy (PCS) on a submicron particle size analyzer (Malvern particle size analyser) at a scattering angle of 90°. A sample (0.5mg) of the nanoparticles suspended in 5 ml of distilled water was used for the measurement (Zhang *et al.*, 2013).

Determination of zeta potential

The zeta potential of the drug-loaded nanoparticles was measured on a zeta sizer (Malvern particle size analyser) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate (Kouchak and Azarpanah, 2015).

Scanning electron microscopy (SEM) of Nanoparticles

From the formulated batches of nanoparticles, formulations (F2) which showed an appropriate balance between the percentage releases were examined for surface morphology and shape using scanning electron microscope Jeol Japan 6000. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 10KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology (Sadiq and Rassol, 2014).

***In vitro* Mucoadhesion Studies**

In vitro mucoadhesion studies of microspheres were assessed using falling liquid film technique. A small portion of the sheep intestinal mucosa was mounted on a glass slide and accurately weighed microspheres were sprinkled on the mucosa. This glass slide was kept in desiccator for 15 min to allow the polymer to interact with the membrane and finally placed in the cell that was attached to the outer assembly at an angle of 45º. Phosphate buffer solution pH 6.4, previously warmed to 37 ± 5ºC was circulated all over the microspheres and membrane at the rate of 1 ml/min. Washings were collected at different time intervals and microspheres were collected by centrifugation followed by drying at 50ºC. The weight of washed out microspheres was determined and percent mucoadhesion was calculated by following formula:

% Mucoadhesion = (Wa-Wl) × 100 / Wa

Where, Wa = weight of microspheres applied; Wl=weight of microspheres leached out.

***In vitro* drug release in gastrointestinal fluids of different pH**

The prepared nanoparticles were evaluated for *in vitro* drug release. The drug release studies were carried out using USP I Basket type dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 100 rpm maintained at 37±0.2°C (Mishra *et al.,* 2017).

A weighed quantity of formulation (equivalent to 10mg) was filled in capsule and kept basket of dissolution apparatus, dissolution media (900 ml, pH 6.4) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 5ml by media. The samples withdrawn were assayed spectrophotometrically at 226 nm for Sumatriptan and using UV visible spectrophotometer. The release of Sumatriptan was calculated with the help of Standard curve of Sumatriptan.

RESULTS AND DISCUSSION

The prepared formulations (F1–F6) of Sumatriptan-loaded mucoadhesive nanoparticles were evaluated for percentage yield, drug entrapment efficiency, and mucoadhesion. As seen in Table 2, the formulation F6 showed the highest percentage yield (83.32%), drug entrapment efficiency ($80.32 \pm 0.54\%$), and mucoadhesive strength ($78.98 \pm 0.85\%$), indicating it as the optimized formulation among all. The increase in entrapment efficiency and mucoadhesion may be attributed to the optimal concentration of chitosan and sodium tripolyphosphate, which contributed to stronger ionic cross-linking and better encapsulation of the drug.

Figure 1 and Figure 2 show that the nanoparticles had a suitable particle size and a desirable zeta potential, suggesting physical stability due to repulsion between particles. Figure 3 (SEM image) confirms spherical morphology and uniform particle distribution in the optimized formulation F6.

Table 3 illustrates the in vitro drug release profile of the optimized formulation in phosphate buffer pH 6.4. The release pattern revealed a biphasic trend with an initial burst release followed by sustained release. At 6 hours, around 93.32% drug was released, and the release continued steadily to reach 99.02% at 12 hours. This pattern is indicative of a controlled release profile, which is advantageous for maintaining therapeutic

levels of Sumatriptan over an extended period.

Regression analysis data (Table 4) showed that the drug release followed a Pappas model (R^2 = 0.9727) more closely than zero-order (R^2 = 0.9485) or first-order (R^2 = 0.9125) kinetics. This suggests that the drug release mechanism is governed by both diffusion and erosion of the polymer matrix, characteristic of mucoadhesive nanoparticle systems.

The study indicates that formulation F6 demonstrates promising characteristics in terms of drug loading, mucoadhesion, and sustained release, making it a suitable candidate for nasal delivery of Sumatriptan.

Table 1: Formulations of the mucoadhasive nanoparticles of Sumatriptan

Batch Code	Sumatriptan (mg)	Chitosan (% w/v)	STPP (% w/v)	PEG (mg)
F1	10	0.5	0.25	5
F2	10	1.0	0.5	10
F3	10	1.0	0.75	15
F4	10	1.5	0.5	10
F5	10	1.0	0.5	20
F6	10	1.0	0.5	15

Table 2: Percentage yield, % Drug entrapment and % Mucoadhesion for different formulation

S. No.	Formulation	Percentage Yield*	% Drug entrapment (w/w)	% Mucoadhesion
1.	F1	78.85±0.35	76.65±0.45	65.85±0.98
2.	F2	76.65±0.45	73.32±0.36	70.36±0.65
3.	F3	75.45±0.36	74.45±0.74	72.25±0.74
4.	F4	79.98±0.45	76.65±0.36	75.45±0.36
5.	F5	74.45±0.25	72.25±0.95	73.32±0.55
6.	F6	83.32±0.63	80.32±0.54	78.98±0.85

***Average of three determinations (n=3)**

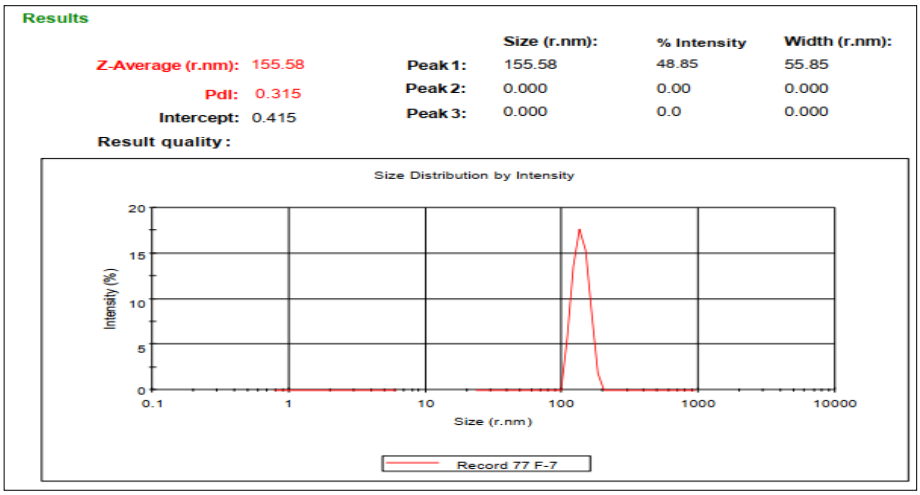

Figure 1: Particle size data of chitosan nanoparticle

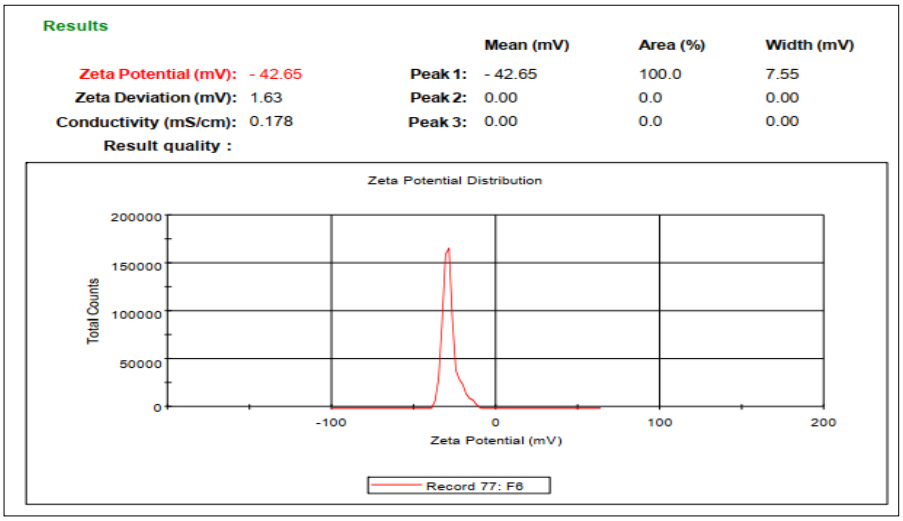

Figure 2: Zeta potential data of chitosan nanoparticle

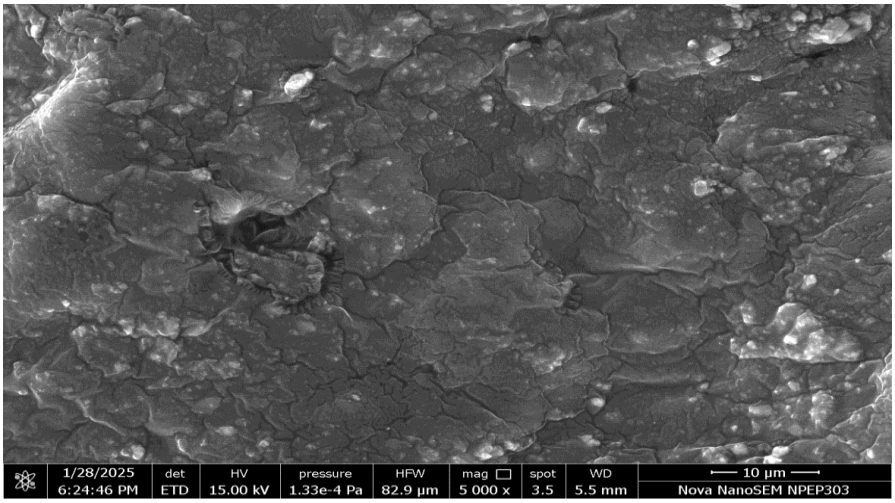

Figure 3: Scanning Electronic Microscopy image of optimized formulation F6

Table 3: Cumulative % drug release of sumatriptan nanoparticles

S. No.	Dissolution medium	Time (hrs)	% Cumulative Drug Release
			Nanoparticle
1	pH 6.4	1	8.85
2		2	13.36
3		3	29.95
4		4	38.78
5		5	55.65
6		6	93.32
7		7	76.65
8		8	85.45
9		9	94.45
10		10	97.88
11		12	99.02

Table 4: Regression analysis data of nanoparticle formulation

Formulation	Zero order	First order	Pappas plot
F6	$R^2 = 0.9485$	$R^2 = 0.9125$	$R^2 = 0.9727$

CONCLUSION

The present study successfully demonstrated that the hydroalcoholic extract of *Lilium candidum* leaves possesses significant antidiabetic potential in streptozotocin-induced diabetic rats. Phytochemical screening confirmed the presence of therapeutically active constituents such as alkaloids, phenols, saponins, and proteins. The extract exhibited a notable hypoglycemic effect, improved lipid profiles, enhanced insulin levels, and reduced glycosylated hemoglobin, with results comparable to the standard antidiabetic drug glibenclamide. These findings scientifically validate the traditional use of *Lilium candidum* in managing diabetes and support its further exploration as a natural, plant-based therapeutic agent for diabetes mellitus.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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